4	ECPA	BEL	General comments	Confounding factors It would be useful if the scientific opinion provided further discussion on the types of potential confounding factors to which farmers are likely to be more highly exposed or affected, compared with the general population. These include: - exposure to cattle, poultry or other farm animals and their housing - exposure to animal infectious diseases (e.g. bird flu, pneumonia) - exposure to farm feed items and the associated dust - exposure to fungal toxins such as aflatoxins - exposure to pollen from various plant species (relevant for respiratory disease or allergy related outcomes) - higher exposure to road dust and radon (common in hilly terrains and associated with lung cancer) - exposure to ultraviolet rays and ozone (due to more labour intensive work during high ozone concentrations) - exposure to soil organisms - exposure to different microbiota (from soil and farm animals) - long/atypical working hours (IARC has recently concluded that shift work has an impact on some hormonal cancers). It is possible that early rising, as normal for farm work, will also impact the biological clock and thereby circadian rhythm controlled biological functions - vitamin D (longer outside hours and leads to higher levels) For each of the above mentioned points, respective literature can be found, e.g. there are now a number of studies which have suggested that poultry breeding is associated with disease risk; Smit et al (2017, pneumonia, DOI 10.1186/s41479-017-0027-0) reported an increased risk for pneumonia infection of residents living near poultry farms. *EFSA Response:* *These confounding factors for farmers have been considered in the Opinion.* *The following text has been added in line 793: "For instance, because agriculture exposures cover many different exposure categories, farmers are likely to be more highly exposed than the general population to a wide array of risk factors, including biological agents (soil organisms, livestock, and farm animals), pollen, dust, sunlight and ozone amongst others, which may act as potential confounding factors".*
5	ECPA	BEL	General comments	Human biomonitoring (HBM) It is not specified how relatively unspecific approaches like 'omics' and 'the exposome' combined with HBM might produce concise results and lead to solid conclusions. The scientific opinion mixes existing HBM methodology (with the limitations discussed) and evolving fields of research such as 'omics' and 'the exposome'. The presentation of the discussion in this way could lead to the perception that these approaches already have the same scientific weight, and might lead to unrealistic expectations. The PPR Panel is balanced and appropriately critical towards their own expectations and proposals (e.g., lines 1427/1428: "However, a truly complete exposome will likely never be measured."), but the discussion of existing methods and potential future developments should be separated. The strengths and weaknesses of the important exposure assessment tool HBM should be reviewed in one place rather than in a scattered way. Some essential aspects such as low specificity of metabolites with different parent compounds (which can also have very different potencies) and the uptake of already existing metabolites instead of

				the parent compound (lines 1047-1055), are easily overlooked. *EFSA Response:* *The comment is noted, but is considered to be more a question of style than scientific context and the draft text is considered appropriate.* A particular issue with the use of HBM data in epidemiology studies is the correlation of short-term exposure markers with long-term health effects. This is all the more difficult as historic exposures can significantly deviate from current exposure, including the spectrum of chemicals and the intensity of exposure, but also co-exposure to unknown substances or substances which are not covered by the scope of the study. Historic HBM data are very rare, and job-exposure matrices are imprecise, as pointed out by the PPR Panel (lines 3408-3410). In this respect, PBPK/TK models will not necessarily help because most chemicals are eliminated with short half-lives in the time range of hours or days. The potential for back-extrapolation is therefore limited. *EFSA Response:* *The issue about correlation of short-term exposures is accepted, as the comment referring to PBPK/TK models (although the draft only mentions the role of PBPK in determining internal or external doses from biological monitoring data).* *The following text has been added in line 1330: "It is particularly challenging to construct an assessment of historical exposures which may deviate from current exposures, in both the range of chemicals and intensity of exposure and also co-exposure to other substances which are not included in the scope of study".* The standardization of HBM with respect to analytical quality and reliability is less strict than in other fields of analytical applications, in particular those who serve regulatory purposes (e.g. food, air, soil or cosmetics). Other scientific panels and expert groups (e.g., the Working Group Analyses in Biological Materials of the Senate Commission for the Investigation of Health Hazards in the Work Area of the German Research Foundation [DFG], and the Human Biomonitoring Commission of the German Federal Environment Agency) have published recommendations for analytical quality criteria for HBM, including interlaboratory comparisons and blinded round robin tests. However, the application of validated HBM methods in other settings than occupational or environmental surveillance studies is not mandatory but depends on project guidelines or scientific quality awareness of the researchers. Therefore, the quality of HBM is very variable, in particular if HBM is not a particular focus of a study. The PPR Panel proposes some minimum standards (e.g., lines 1305–1314). *EFSA Response:* *The PPR Panel simply reports the existing standards that apply to analytical methods for monitoring that applicants are required to submit for approval. The following text at lines 1318-1321 point out that it is important those contemplating future studies demonstrate validity of the methods to be employed.*

6	ECPA	BEL	General comments	Human biomonitoring (HBM) Published background concentrations for a number of chemicals in biological materials, so-called 'reference values' for the general population (German Federal Environment Agency) or Biological Reference Values BAR (DFG) for occupationally non-exposed workers, reveal a high variability of results, strongly influenced by the choice of analytical instrumentation (or year of study) and by country or subgroup (urban/rural). Important influence factors such as age, gender or smoking need to be considered. Additionally, the reported units and standardization of measurements differ from study to study (e.g. no dilution adjustment versus creatinine adjustment versus cotinine adjustment for urinary measures, µg/L, µg/dl). Some studies acknowledge, in example, that the World Health Organization (WHO), among others, recommends the exclusion of very diluted or concentrated urine samples (for adults, not children). Furthermore, the presentation of statistical data is extremely variable in epidemiology evaluations (e.g., arithmetic or geometric mean, standard deviation or standard error, median values, different percentiles, number of results below the limit of quantification (LOQ), and the mathematical treatment of nondetects), which can complicate integration of results across studies. In this respect, the scientific opinion should outline specific standards and basic requirements with regard to analytical quality criteria for HBM and for data presentation. These points are adequately addressed within the document, but there is no coherent recommendation (e.g. a specific annex). *EFSA Response:* *This is an interesting comment, but this is beyond the ToR of the opinion. The issues are discussed in the outsourced HBM project and readers would be direct to that.* *The following text has been added in line 1385: "Further discussion on quality assurance issues and factors to consider in relation to HBM studies is present in the report of the EFSA outsourced project (Bevan et al, 2017)."*
7	UCLA	USA	General comments	I am an environmental epidemiologist and expert in the area of pesticide research. I have served for the United States Institute of Medicine (IOM) National Academy of Sciences for decades including on pesticide related reviews and risk assessment reports. I teach environmental and occupational epidemiology in one of the premier teaching institutions and have conducted NIH funded research on pesticide health effects for more than 2 decades. I consider this EFSA document not only a badly written document but a general attack on epidemiology as a science by non-epidemiologists. The statement that "Despite the considerable amount of epidemiological information available, the quality of this evidence is usually low and many biases likely affect the results to an extent that firm conclusions cannot be drawn" is completely unsubstantiated and contrary to my reading and interpretation of this literature. The "major methodological drawbacks: study designs prone to bias, poor exposure characterisation, inadequate health outcomes, deficiencies in statistical analysis and poor quality of reporting of research findings" mentioned in line 22 may affect some but certainly not all of the studies on pesticide health effects that are published. This broad generalization across all studies should either be considered as uninformed or malicious in intent and is not supported by the fact that many such studies have been published in highly regarded peer-reviewed journals. Also, the statement on line 974: "Apart from the Agricultural Health Study, there were no other large studies with good quality data for many study outcomes" is plainly wrong; there are a number of other good quality and large studies (note large should refer to the number of outcomes observed not the total number of subjects enrolled!) and some of even better quality i.e. larger studies with more comprehensive exposure and

				outcome assessment for some outcomes such as Parkinson's disease. But more importantly, if the authors think so highly of the AHS study, why do they then in their summary reject all epidemiologic evidence as flawed?. That this report is most an unsubstantiated attack on human observational epidemiology studies that uses out of context quotes and judgements is further underlined by the statement in lines 1182-84 " It is widely accepted that biomedical research is subject to and suffers from diverse biases. Chalmers and Glasziou (2009) have estimated that approximately 85% of research investment in this area is wasted. An assessment of weaknesses in the design, conduct, and analysis of biomedical and public health research studies is essential to identify potentially misleading results and identify reliable data." I went back to the cited paper by Chalmers and Glasziou (2009) and found that this statement is a broad and malicious indictment of pesticide epidemiology based on a completely different type of data i.e. Chalmers and Glasziou were evaluating clinical trials data; indeed, they concluded that "although we have mainly used evidence about the design and reporting of clinical trials, we believe it is reasonable to assume that the problems also apply to other types of research" but did never state what types of research this would be (could include all applied sciences including toxicology). Thus, they only analyzed the type of data and design that the EFSA report authors are calling their gold standard i.e. clinical trial in human subjects and find these studies indeed greatly lacking in scientific approach and validity. *EFSA Response:* *This comment misunderstands the scope of the Scientific opinion, which is related only to epidemiological studies on pesticides, not on any other chemical substances, and also under the framework of the EU regulation on pesticides approval.* *The sentence quoting Chalmers and Glasziou (2009) relates to biomedical research investment (in particular controlled trials) but not specifically to environmental epidemiology (see comment 73).* *The sentence in line 1182 quoting Chalmers and Glasziou has been deleted to avoid misunderstanding.* *Line 974 has been modified to read "Apart from the Agricultural Health Study and other similarly designed studies".* *The Opinion has been revised to tone-down the limitations of pesticide epidemiological studies, if necessary.*
8	personal	USA	General comments	The purpose of this report is unclear. The stated purpose is to discuss methodological limitations affecting the quality of epidemiologic studies on pesticides and recommendations in how to improve them, as well as a framework on how to integrate the complementary information from epidemiology and other disciplines (e.g., toxicology). I think that the latter point is an important one because clearly toxicologic and other mechanistic data are important elements in both determining causality and for conducting risk assessment. However, the vast majority of the document refers to weaknesses/limitations in epidemiologic studies in general. Indeed, there are discussions of the superiority of interventional studies, which are clearly unethical in evaluating pesticides and human health. Since so much of the document is devoted to how to improve upon epidemiologic studies in general, it seems a deficiency that the document appears to be have been written by a panel with essentially no epidemiologists. It seems that excluding the practitioners of the discipline of which the report is mostly evaluating is a severe limitation of this exercise, and there are many statements throughout the document where the exclusion of this expertise from the panel is evident. For example, there are several statements that are not entirely accurate describing epidemiologic principles. Design principles are also laid out in black and white terms, which ignores the nuances related to the question being asked, and what the optimal design considerations are for the particular question. For example, there are blanket statements about the utility and quality of specific study designs, (e.g.,

				case-control studies) that in some cases may be the only practical way to conduct a study among people (for example, for rare outcomes) where elsewhere there are multiple cautions against small sample sizes, for which the results can't be trusted, even if they find an association because of effect size magnification. Potential limitations or biases are presented in such a way that a reader might think that all studies suffer from all of them. In addition, the panel proposes a number of "refinements" to future studies to be useful to risk assessment, some of which are good ideas, and are being considered and incorporated into ongoing research and some of which are unproven at best. It seems to me that if the goal of this document were to discuss how to integrate epidemiology into risk assessment for pesticides an example where this was actually done successfully might be given, rather than just listing all of the potential limitations of epidemiology in general. As written, the reader is left with the impression (intentional or not) that this panel does not believe that epidemiology can or should be integrated into risk assessment successfully. *EFSA Response:* *The purpose of the Opinion is clearly mentioned in section 1.2 "Terms of Reference" (ToR), which are equivalent to its objectives. The first ToR is to collect and review all sources of gaps and limitations of epidemiological studies on pesticides, but not of epidemiologic studies in general. This opinion does not mention interventional studies on pesticides which are not only unethical but are also forbidden in the EU regulation.* *The Working Group set up to draft this Opinion was comprised by three epidemiologists with different background and one additional member with publications in peer-reviewed journals on occupational and environmental exposure to pesticides and diverse health outcomes. Yet, it is important to keep in mind that those on the receiving end, who uses these studies, were also involved and they rightly pointed out many of the difficulties faced when using these studies. The point is that there is both room and need for improvements and researcher should take that seriously. Other factors such as better sharing of information and better registration of information that could assist researcher to do better studies are also needed.* *See otherwise our response to your previous comments (some changes have been made in order to make out point more balanced).* *Chapter 2 is devoted to general principles of epidemiological studies under the view of the WG and the PPR Panel. The Panel is pretty confident of the important advantages of epidemiological studies on pesticides, but also acknowledges that the EU regulation requires recognised standards for these studies to be of particular value for risk assessment. On the other hand, the integration of epidemiological evidence with other lines of evidence on pesticides is part of the fourth ToR, but not the main one.* *As a final comment, for your information there is not a good example where epidemiology has been successfully integrated into the regulatory risk assessment of pesticides within the EU context for the time being.*
9	National Institute of Occupational Health	NOR	General comments	As an epidemiologist, I have read the Panel Report with great interest. The Report presents a thorough description of limitations connected with epidemiological studies, and gives some advices on how to overcome these limitations. There are, however, several general subjects on which I would like to comment. The Panel has given no rationale for a separate evaluation of epidemiology in the field of pesticides in contrast to other chemicals. In 10my opinion, the principles for the use of scientific evidence in human regulatory toxicology are the same for all chemicals, and all the limitations of epidemiology outlined in the Panel Report are, and have